demic and the quantification of the impact of such an epidemic in terms of sick leave.

The development of tools, currently in progress, will permit the use of the same method on a regional basis. The tool described here, in association with other methods developed at our center[8] will allow the prospective prediction of future epidemics and assessments of their economic impact with reasonable accuracy. □

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Antibiotic Use among Children in an Urban Brazilian Slum: A Risk Factor for Diarrhea?

John B. Schorling, MD, MPH, Maria Auxiliadora De Souza, MD, and Richard L. Guerrant, MD

ABSTRACT

Among a cohort of children in a poor urban setting in Brazil, the relative risk for the occurrence of a new episode of diarrhea in the two weeks following antibiotic use vs all other weeks was 1.44 (95% confidence interval (CI) = 1.33, 2.45). Among children never exposed to antibiotics, the odds ratio was 1.34 (95% CI = 0.84, 2.16) after stratifying by individual child and controlling for previous diarrhea. Further research is needed to confirm whether antibiotics are a risk factor for diarrhea in such settings. (*Am J Public Health* 1991; 81:99–100)

Introduction

Antibiotics are commonly used and can be obtained without prescription in many developing countries.[1] Although antibiotics are valuable treatments of many infectious diseases, they are not without risk. Potential problems associated with their use include the selection of resistant bacteria[2] and the development of serious side effects, including antibiotic-associated diarrhea.[3] Furthermore, the use of antibiotics has been documented to predispose to symptomatic *Salmonella* gastroenteritis.[4] We therefore hypothesized that antibiotic use might be a risk factor for diarrhea among a cohort of children in a community setting where the likelihood of exposure to infection was high.

Methods

This study was part of an illness surveillance project[5] undertaken from 1984 to 1986 in a three block area of a slum in the northeastern Brazilian city of Fortaleza, which has a population of nearly two million. Thrice weekly visits were made by trained community health workers to the homes of a cohort of children less than five years of age. At each visit, a history of any diarrhea since the previous visit was obtained from the caretaker of each child. Diarrhea was defined as an increase in stool frequency or decrease in consistency as noted by the caretaker. At least three diarrhea-free days separated episodes.

Antibiotic use was determined over a 16-week period (January-April 1986) by weekly visits by one of the authors (JBS) to each of the 45 homes of the 105 children enrolled in the cohort at the time. A standardized questionnaire was employed to obtain information concerning antibiotics used by the children during the previous week. An antibiotic course was defined as one or more doses of a drug, given at least daily with less than two days interruption.

From the Division of Geographic Medicine, University of Virginia, Charlottesville; and the Department of Social Medicine, Federal University of Ceara, Fortalez, Ceara, Brazil. Address reprint requests to John B. Schorling, MD, MPH, Box 494, Department of Medicine, University of Virginia Health Sciences Center, Charlottesville, VA 22908. This paper, submitted to the Journal February 5, 1990, was revised and accepted for publication May 19, 1990.

Results

A total of 65 children took 137 courses of antibiotics during the 16-week period of study. Each week an average of 8.6 children (82/1000/week) began a course of antibiotics. The most frequently used drugs were erythromycin, penicillins, tetracyclines, and trimethoprim-sulfamethoxasole. Antibiotics were taken for an average of 5.3 days.

During the study period, 349 episodes of diarrhea occurred among the children in the cohort (an average of 10.8 episodes per child-year). The occurrence of diarrhea following the use of antibiotics was determined during the final 14 weeks of observation. Episodes of diarrhea during the first two weeks were excluded since preceding antibiotic use had not been prospectively determined. A period of two weeks following antibiotic use was arbitrarily chosen as the time at risk.

There were complete data for 1096 of 1470 weeks (75 percent) of observation. Following a course of antibiotics, a new episode of diarrhea occurred in 28 percent of the initial weeks after their use, in 32 percent of the second weeks, and 22 percent of the third weeks. Overall, a new episode of diarrhea occurred in 55 of the 194 weeks (28.3 percent) which were within two weeks of antibiotic use, and 177 of the 902 weeks (19.6 percent) not within two weeks of antibiotic use. The relative risk of diarrhea within two weeks of antibiotic use versus other weeks was 1.44 (95% confidence interval [CI] 1.11, 1.89).

The risk of diarrhea was also related to age in yearly increments (odds ratio 0.7, 95% CI = 0.6, 0.8), whether or not diarrhea occurred in the previous two weeks (odds ratio 2.3, 95% CI = 1.6, 3.4), and whether or not the child ever took antibiotics during the 14-week period (odds ratio 1.8, 95% CI = 1.3, 2.4). Previous diarrhea and ever taking antibiotics were also related to antibiotic exposure, but age was not, as 16 to 17 percent of the weeks in each yearly group followed antibiotic use.

The data from children at risk (i.e. who had ever taken antibiotics) were therefore stratified according to whether or not diarrhea occurred during the preceding two weeks. Each child was also considered a separate stratum, since the weeks of observation for each child were not independent. The odds ratio (Mantel-Haenszel) for diarrhea in the two weeks following antibiotic use when stratified by these variables was 1.34 (95% CI = 0.84, 2.16). A logistic regression model, which included previous diarrhea but did not consider each child separately, resulted in an odds ratio of 1.35 (95% CI = 0.89, 2.04).

Discussion

Diarrhea was more common in the two weeks following antibiotic use than in weeks not following such use after stratifying by individual child and controlling for preceding diarrhea. The odds ratios from the stratified and multivariate analyses were quite similar to the overall relative risk, although the confidence intervals of the former included 1.0. However, only 350 weeks were included in the stratified analysis and 550 in the logistic model, versus 1096 in the initial analysis. All the point estimates were quite similar, suggesting that a true association existed.

The definition of diarrhea used in this study was based on the caretaker's subjective report, and the number of diarrhea episodes noted may have been higher than would have been found using stricter criteria. However, 94 percent of the stool samples collected from children in this cohort reported to have diarrhea were liquid, and over 50 percent yielded pathogenic organisms.[5] These findings support the use of this definition as a valid indicator of diarrheal illness.

Diarrhea has been reported following the use of antibiotics in other settings.[6,7] However, antibiotic use is not usually considered a risk factor for diarrhea in prospective, community studies of children. Because of the widespread use of these agents in underdeveloped areas, our results suggest that they may be responsible for some proportion of diarrheal illness. If there were an increase in diarrhea due to antibiotics that was approximated by the stratified odds ratio we obtained (1.34), antibiotic use could be responsible for 25 percent of all diarrhea in exposed children.[8]

There are many potential causes of diarrhea following the use of antibiotics.[3] These include the selection of resistant pathogenic organisms, the overgrowth of organisms which may be present normally, such as *Clostridium difficile*, and the eradication of normal flora. Further work is needed to determine if antibiotics do contribute to the diarrheal illness burden of children in settings such as this and, if so, to elucidate the possible mechanisms. □

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